Haemophilia (2004), **10**, 413–421 DOI: 10.1111/j.1365-2516.2004.00919.x

REVIEW ARTICLE

Liver biopsy in patients with inherited disorders of coagulation and chronic hepatitis C

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Summary. Liver biopsy plays a pivotal role in the management of patients with a variety of liver diseases, including chronic hepatitis C virus. The major risk of the procedure is the potential for significant haemorrhagic complications. Although the data are limited, the procedure does not appear to pose excessive risk to the patient with inherited disorders of coagulation, provided that adequate haemostasis can be achieved prior to the liver biopsy. This requires close coordination of care between the hepatologist and the haematologist. Indications for liver biopsy should be the same in patients with haemophilia as in other populations.

Keywords: complications, haemophilia, hepatitis C, liver biopsy

Introduction

Hepatitis C virus (HCV) is a significant cause of acute hepatitis and chronic liver disease worldwide. In the United States (US), the most robust data on the prevalence of HCV come from the third National Health and Nutrition Examination Survey (NHANES III), a survey of the non-institutionalized civilian population conducted by the Centers for Disease Control Prevention (CDC) between 1988 and 1994 inclusive. The study used a complex, stratified, multistage probability-sample design adjusted to represent a distribution of subjects similar in age, gender, educational level, race and ethnicity to the US population as a whole. The CDC estimated that the prevalence of antibodies to HCV in the US is 1.8%, of which 74% have chronic infection [1]. The true prevalence of chronic infection in the US, however, is undoubtedly much higher than suggested by the CDC estimate because several high risk groups (incarcerated, homeless, institutionalized) were not included in the study.

Transmission of HCV is predominantly through exposure to contaminated blood. As a result, risk factors for HCV acquisition reflect the predilection of the virus for the parenteral route. Injection drug use remains the most common risk factor cited among persons with chronic HCV, but prior to 1992, transfusion recipients of infected blood and blood products were also at great risk of acquiring HCV. The prevalence of antibodies to HCV in injection drug users is estimated to be as high as 70–85% [2–5]. Patients with haemophilia who were treated with non-viral inactivated clotting factors have a prevalence rate of hepatitis C, estimated to be as high as 90% or more, that is unmatched in any risk group [2,6–8].

Despite the disproportionate rate of HCV infection, there have been few studies in the US of the natural history of this disease in patients with haemophilia. Clinicians have long recognized that the clinical spectrum of chronic hepatitis C varies considerably and the development of complications

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Accepted after revision 21 April 2004

related to liver disease is unpredictable. The hallmark of advanced liver disease and prelude to complications of portal hypertension and hepatocellular carcinoma is the development of fibrosis and cirrhosis. The ability to accurately stage the extent of liver involvement in chronic HCV is paramount to the conduct of interpretable natural history studies. Although there are a number of explanations for the paucity of natural history studies in patients with inherited disorders of coagulation, chief among them may be the reluctance of clinicians to perform liver biopsies in this special population. This reluctance is in large part the result of the perception that liver biopsy may incur a significant risk of bleeding.

Liver biopsy in the general population: evolving role in HCV management

It is widely accepted that liver biopsy plays a pivotal role in the management of patients with a variety of liver diseases. Proponents of the procedure cite several reasons to justify its use in the care of patients with chronic HCV. One commonly referenced reason is that examination of liver histology is useful in confirming the clinical diagnosis [9]. Admittedly, this has become a less convincing argument for the use of the procedure. Antibody tests and nucleic acid amplification technologies definitively document the presence of chronic HCV and other serologic assays help to exclude competing diagnoses in the overwhelming majority of clinical conundrums. For example, serum iron studies can usually exclude the diagnosis of iron overload states. Likewise, Wilson's disease and α-1-antitrypsin deficiency are unlikely causes of liver disease if the appropriate serum tests are normal. In point of fact it is rare that the liver biopsy uncovers an unexpected diagnosis during the evaluation of patients with suspected hepatitis C. Nevertheless, liver biopsy does provide final confirmation of the working diagnosis.

More relevant, however, is the role of liver biopsy in evaluating the potential contribution of concomitant disease processes [8,9]. While abdominal imaging studies may provide information on iron overload and steatosis in the liver, they are insufficient to characterize the extent of involvement; and only liver biopsy can evaluate coexisting alcoholic liver disease. In reality the major purpose of liver biopsy in the management of HCV is to assess the severity of necroinflammation (grade) and the extent of fibrosis (stage). Such examination of histological grade and stage has yielded insights into the natural history of chronic HCV and resulted in valuable prognostic information for patients with HCV.

Progression of liver fibrosis was evaluated in a cross-sectional study of European patients who had been enrolled in several large antiviral treatment protocols [10]. Three groups of patients were identified who had median rates of development of fibrosis varying from 20 years or less (in 33% of patients) to those who were unlikely to develop cirrhosis even with 50 years of actuarial follow-up (31%). One-third of the participants studied were felt to have an average rate of cirrhosis developing 30 years after HCV infection. Alcohol consumption greater than 50 g per day was one of three independent risk factors (including older age at acquisition and male gender) associated with more rapid progression of fibrosis [10]. There was no association between viral characteristics and fibrosis. Although this study was very carefully designed, the duration of infection, a critical component needed to calculate fibrosis progression, could be established with some certainty in only 52% of the cohort based upon the identification of risk factors and patient medical histories. Yano *et al.* used information from liver biopsies to evaluate the association between initial biopsy and development of cirrhosis at a later date. Despite the relatively small sample size of the study, the authors clearly demonstrated a correlation between moderately advanced histology at presentation and likelihood of having cirrhosis in the future [11]. Such studies have been instrumental in illuminating the natural history of liver disease progression in patients with chronic hepatitis C [10,11].

The prognostic information gained from liver biopsy may allow patients and their providers to more adequately weigh the risks and benefits of antiviral therapy for HCV [12]. For example, a patient with HCV genotype 1 and mild histology may decide to defer treatment given the sustained virologic response rates and the side-effect profile of available antiviral regimens. As alternative therapies will not be available for many years, a patient with moderate or advanced fibrosis may decide to initiate treatment and remain on treatment in spite of the side-effects. In contrast, individuals with HCV genotype 2 or 3 may decide to forgo the liver biopsy and elect to be treated because of the high likelihood of a sustained virologic response and the shorter duration of treatment compared with other HCV genotypes.

Liver biopsy is commonly used in HCV antiviral treatment studies to assess the effect of the therapeutic intervention on hepatic histology. While necroinflammation is much more responsive to treatment, paired pretreatment and post-treatment liver biopsies clearly demonstrate a reduction in

fibrosis in patients who have successfully eradicated the virus [13,14]. Post-treatment liver biopsies are generally not indicated in routine clinical practice, but there are occasions when the histological information is useful, e.g. in patients who want to consider maintenance interferon therapy.

Techniques of liver biopsy

There are a number of approaches used in the performance of the liver biopsy. The percutaneous approach is very accessible in routine practice settings and most widely used. Percutaneous liver biopsy is usually performed by gastroenterologists, hepatologists or radiologists. In many centres percutaneous liver biopsies are performed using ultrasound to mark an ideal site for the biopsy or to guide the operator during the conduct of the procedure. The patient is placed in the supine position. After the desired site has been identified, the patient is prepped and draped in the usual manner. A local anaesthetic is applied and an incision is made to allow passage of the biopsy needle. With the patient at end-expiration, the biopsy device is used to obtain a core of tissue. The procedure may be repeated if an inadequate specimen is obtained. The patient in then monitored for signs of complications. The procedure may be performed with or without the use of conscious sedation.

In settings where vascular interventional radiologists are available, transjugular liver biopsies are often performed under conscious sedation. The patient is placed in the supine position. A catheter is introduced into the external jugular vein. The right hepatic artery is catheterized and the catheter position is confirmed under fluoroscopic guidance. A guide-wire is advanced through the catheter and a sheath with an inner metal cannula is inserted into the right hepatic vein. A core biopsy needle is advanced through the sheath to obtain a sample of tissue. Three to five passes are usually required to obtain sufficient tissue for histologic examination. After removal of the sheath and cannula, the puncture site is compressed to achieve haemostasis. Although the procedure may also be performed laparoscopically, this approach is less commonly employed.

Numerous studies have attempted to define the nature and rate of complications associated with liver biopsy. Regardless of the technique employed, the overall risk of serious adverse events is low [12,15–19] (Table 1). As a result, it has not been feasible to compare the relative complication rates among the different techniques. Needles for percutaneous liver biopsy fall into two main categories, suction needles (Jamshidi, Menghini, Klatskin) and cutting needles (Tru-cut, Vim-Silverman). Cutting needles may also be spring-loaded for use in an automated device. Obviously, the major concern with the procedure is the risk of bleeding complications. Cutting needles may have a slightly higher rate of haemorrhage compared with suction needles [15]. However, suction needles are more prone to fragmentation than cutting needles when cirrhosis is present [12].

Table 1. Major complications of liver biopsies.

Complication	Incidence (%)	Haemophilia
Pain (moderate/severe) [30]	6	
Haemorrhage		
All severity [15,18,30,39]	1.0–1.7	3.3% (0–12.5)*
Requiring transfusion [30]	0.7	
Death [12,15,16]	0.01–0.33	0.33%

*12.5 in Aledort *et al.* In 400 patients reported since then rate is 0.25%.

There are few absolute contraindications to percutaneous liver biopsy. Those that do exist are conditions that increase the risk of bleeding complications, such as, an uncorrectable coagulopathy, ascites, an uncooperative patient, or the inability to identify an appropriate site free of masses or vessels. In general, the procedure should not be performed if it will not affect or influence management in any way. Although there are certainly exceptions, routine use of liver biopsies in patients with decompensated liver disease or obvious signs of cirrhosis may not be warranted.

Liver histology: grading and staging

Despite the acknowledgement that liver biopsy is important in the management of chronic HCV and other liver diseases, there is no universally accepted scoring system for evaluation of liver histology. There are no fewer than five systems proposed in the medical literature [9]. The three most commonly used in research settings are the Knodell [20], Metavir [21,22], and the Ishak Modification to the Knodell [23]. A number of studies have been conducted to evaluate the inter- and intraobserver variability in interpretation of hepatic histology. The studies demonstrate good concordance using the different systems [22,24,25].

The necroinflammatory component of the scoring systems is referred to as the grade, and it assesses portal inflammation, interface hepatitis and lobular inflammation. It is believed that the grade reflects ongoing activity and is more sensitive to treatment. Stage refers to fibrosis and the vascular and parenchymal remodelling of liver tissue that occurs

in the long-term. It is not entirely clear that the level of detail used in these scoring systems is necessary for routine clinical use [9]. What is clear, however, is the need for an experienced pathologist to interpret the biopsy specimens. Bejarano *et al.* have demonstrated that a significant number of biopsies from community pathologists had major discrepancies when compared with evaluations of expert hepatohistopathologists [26].

Accurate interpretation of liver histology is predicated on the notion that diseases such as HCV affect the liver more or less in the same manner throughout. Thus the biopsy specimen is assumed to be representative of the whole liver with respect to evaluation of grade and stage. Pathologist agree that sufficient tissue is needed to make a confident assessment of the hepatic histology, but there is no agreement as to the minimum size of the biopsy or the minimum number of portal areas necessary to achieve a firm diagnosis. In general a specimen that measures 1–2 cm in length and has 6–10 portal tracts should be satisfactory.

Liver biopsy in patients with haemophilia and HCV: review of the literature

Haemophilia is often cited as a relative contraindication to liver biopsy [12]. The 1997 National Institutes of Health Consensus Development Conference on Management of Hepatitis C advised against liver biopsy in patients with haemophilia because of excessive risk to the patient [27]. It is easy to understand the concerns that lead to such statements, but one must consider whether the available data justify such an admonition. Aledort *et al.* evaluated retrospectively the outcome in 126 liver biopsies in patients with haemophilia [28]. The study consisted of a questionnaire of all major haemophilia treatment centres listed in the World Federation of haemophilia in the US and western Europe and any other institutions known to the investigators personally or by way of published manuscripts. All biopsies performed through January 1981 were included in the report. Study participants reported a 12.5% morbidity rate, i.e., prolongation of planned hospitalization or substantial increase in coagulation factor replacement beyond what had been planned for the procedure in order to control bleeding. The study did not require documentation of bleeding. Moreover, there was no standard amount for how much factor was to be used. Thus, it is possible that centers could have used extra factor in the absence of significant hemorrhage. No fatalities occurred in the study, but the authors did comment that they were aware of two unreported deaths following liver biopsy, a fatality rate of more than 1%. These anecdotal deaths undoubtedly had a significant effect on the perception of risk of bleeding complications from liver biopsy in the setting of haemophilia and other inherited disorders of coagulation.

One of the two unreported deaths cited in the Aledort study [28] was later described in more detail. It is worth reviewing the events surrounding the death to better understand whether or not haemophilia *per se* was the primary factor contributing to the death. In a letter to the editor, Lee [29] describes a patient with haemophilia A (the report does not mention whether or not the patient had an inhibitor) who developed acute jaundice with non-A non-B hepatitis in September 1972 after having received unsterilized large-pool factor VIII 3 months earlier. The patient had intermittent bouts of cholestatic jaundice in the ensuing 8 years and he underwent a liver biopsy in October 1980 for further evaluation. Following the procedure, the patient bled into the abdomen and was taken to the operating room where a torn capsule was noted. He required hepatic artery ligation massive transfusion of whole blood, platelets, fresh frozen plasma, and FVIII concentrate to stop the bleeding. Because of continued haemorrhage 3 days after the procedure, he was taken back into the operating room for laparotomy and a right haemihepatectomy. The patient's course was further complicated by renal failure requiring haemodialysis. He died 8 days after the liver biopsy. The author did not provide details about the liver biopsy procedure itself (technique, instrument, experience of operator, haemostasis protocol, etc.) that may have contributed to the poor outcome. Nevertheless, one can argue that the torn capsule (a rare but potentially serious complication even in patients without haemophilia) led to the outcome and not haemophilia *per se*.

Since the publication of the series in 1985, there have been several case series of liver biopsy in patients with haemophilia. The studies tend to be reports on a small number of biopsies, ranging from 6 to 103. The approach used for the biopsy also varied, including percutaneous liver biopsies, ultrasound guided percutaneous liver biopsies, transjugular liver biopsies and laparoscopic biopsies (Table 2). No bleeding complications were reported in any of these studies, with the exception of one case of haemophilia. In contrast to the report by Aledort, no fatalities have been documented in these series. Over 600 liver biopsies in haemophiliacs have been reported in the medical literature since the 1970s. With the exception of the fatalities noted by Aledort in 1985, we are not aware of any others. Thus the calculated complication rate in haemophiliacs

Table 2. Selected studies including liver biopsies in patients with haemophilia.

Reference	No. of biopsies	Method	Haemostasis	Outcome
DiMichele [38]	13	Transjugular	Factor prior to biopsy to attain level of ≥0.7 IU mL^{-1} through 24 h, ≥0.5 postoperative day 3 and ≥0.3 postoperative days 4/5	No bleeding. Three patients with pain. 1–2 days admission
Lethagen [40]	55	Ultrasound guidance. Tru-Cut	Factor to attain 100% levels prior to biopsy. Maintain normal level for 2 days postbiopsy. Moderate/severe haemophilia 20–30 IU daily for 1 week. All received tranexamic acid 10 mg kg^{-1} i.v. 30 min prior to biopsy and 25 mg kg^{-1} p.o. t.i.d. for 7 days	No bleeding. 2 days admission
McMahon [37]	23	Menghini or ultra sound guidance and automated device	Factor to attain 100% levels prior to biopsy. Intermittent bolus or continuous infusion used to maintain 100% level for 2 days postbiopsy. Some patients received tranexamic acid (2 g day^{-1} for 10 days)	No bleeding. Two patients with pain. 3 days admission
Shields [41]	21	Not specified	Not specified	No bleeding complications reported
Venkataramani [36]	13	Ultrasound marked. Microvasive gun	Factor to attain 100% levels prior to biopsy. Intermittent bolus or continuous infusion used. Regular factor infusion for 1 week after discharge	No bleeding. One patient with pain 24 h after discharge. 1–2 days admission
Adamowicz [42]	13	Not specified	Factor 1 h prior to biopsy to attain levels of 1.0 IU mL^{-1} (FVIII) or 0.8 IU mL^{-1} (FIX). Patients retreated at 12 and 24 h postbiopsy to attain levels of 1.0/0.8 IU mL^{-1}. Factor levels 48 h postbiopsy 0.5/0.5 IU mL^{-1}	No bleeding. 10 days admission
Farrell [43]	6	Ultrasound guided. ASAP gun	FVIII infusion to 100% levels prior to biopsy and maintained at 100% (4 U kg^{-1} h^{-1}) for 48 h postbiopsy by continuous infusion	No bleeding. 2 days admission
Fukuda [44]	36	Not specified	40–60 U kg^{-1} factor concentrate 1 h prior to biopsy. 50% initial dose at 12, 24 and 48 h postbiopsy	No bleeding
Wong [35]	35	Ultrasound guided Tru-Cut needle	FVIII or FIX infusion to attain 100% levels prior to biopsy. Factor level >50% for 36 h postbiopsy by bolus or continuous infusion	No bleeding. 2–4 days admission
Gupta [45]	6	Transjugular	Not specified	No bleeding. 24 h admission
Ahmed [46]	50	Percutaneous. Menghini. No ultrasound guidance	FVIII or FIX infusion to 100% levels prior to biopsy. Factor level >50% maintained for 48 h postbiopsy	No bleeding. Two patients re-admitted for pain around biopsy site. 24 h admission
Makris and Preston [34], Makris [47]	103	Not specified	Factor 1 h prior to biopsy to attain levels of 1.0 IU mL^{-1} (FVIII) or 0.8 IU mL^{-1} (FIX). Patients retreated at 12 and 24 h postbiopsy to attain levels of 1.0/0.8 IU mL^{-1}. Factor levels 48 h postbiopsy 0.5/0.5 IU mL^{-1}	1 haemobilia
Hanley [48]	23	Laparoscopic. Tru-Cut needle	Factor 2 h prior to biopsy to attain postinfusion levels of 1.0 IU mL^{-1} (FVIII) or 0.7 IU mL^{-1} (FIX). FVIII/IX levels maintained between 0.5–1.0/0.5–0.7 IU mL^{-1} for 48 h and infusions continued for 4 days after biopsy	No bleeding. One unsuccessful because of inadequate sedation 4 days admission
Aledort [28]	126	Not specified	Not specified	12.5% bleeding; two deaths reported anecdotally
Total	513	N/A	N/A	1 haemobilia 16 bleeding

(0.33%) may not be different from studies in non-haemophiliacs [30].

The reasons for the discrepancy between the report by Aledort and subsequent series are not entirely clear. One possibility may be the technical expertise of the clinician performing the procedure. Froehlich *et al.* [31] have noted fewer complications among physicians who perform more than 50 procedures yearly. Another potential explanation for the deaths reported by Aledort *et al.* may be the protocol used for haemostasis and the length of hospital stay. Unfortunately, the studies are too small to adequately assess the hypothesis. Different studies used intermittent bolus infusion or continuous infusion. Generally, the goal was to provide enough factor concentrate to achieve a level of 1 IU mL^{-1} (100%) before the procedure and enough factor for 50% coverage through postprocedure day 3. Some centres used tranexamic acid while others did not. The length of hospital stay ranged from 24 h to 3 days in most institutions.

Overall, the literature supports the notion that patients with inherited disorders of coagulation can safely undergo liver biopsy provided that proper precautions are taken. Thus these patients should be managed similar to other groups with viral hepatitis. As described earlier, it is widely accepted that the prognostic information gained from liver biopsy may allow patients and their providers to more adequately weigh the risks and benefits of antiviral therapy for HCV [12]. One should be cautious when applying algorithms to different patient groups. HCV/HIV co-infection is common in the haemophilia population and trials of pegylated interferon and ribavirin suggest that patients with HIV/HCV co-infection do not have the same sustained virologic response rates seen in patients with HCV mono-infection. In fact, the reponse rates for patients with HIV/HCV dual infection and non-1 genotypes is only 50% [32], not much better that genotype 1 in individuals with HCV mono-infection. As a result, all patients with HIV/HCV dual infection should be considered for liver biopsy if there are no contraindications.

Areas for future research

One significant difference between liver biopsies in the general population and patients with haemophilia is the cost of the procedure [33]. The cost of factor replacement alone can be greater than the total cost of the procedure in patients without coagulation disorders. Lee [29] estimated that factor replacement to cover the procedure would cost £7000, although this has been disputed by Makris and Preston [34], who suggest that the cost of biopsy in a 70 kg patient with severe (<0.01 IU mL^{-1}) haemophilia is less than £3000. This estimate is much more in line with Wong *et al.* [35]. These studies may not have included all the costs associated with liver biopsy in patients with inherited disorders of coagulation. Obviously, inpatient and monitoring costs also add to the expense of the procedure. Venkataramani *et al.* [36] directly compared existing billing records on the 13 patients with haemophilia and 10 non-haemophiliac outpatient liver biopsies performed around the same time. Mean biopsy and hospital-associated charges for the 13 haemophilia patients in the series were $5000. Outpatient biopsy charges for non-haemophiliac patients in the same period averaged $1500. All the biopsies were performed with ultrasound marking and an automated biopsy device. Clearly, the cost of liver biopsy is significantly more expensive in this population. Cost-effectiveness studies are needed to address the use of biopsies in this population, taking into account the value of the prognostic information gained from the liver biopsy.

There is a debate over the relative merits and safety of percutaneous liver biopsies and transjugular liver biopsies. All the procedures provide adequate specimens. Each technique has advantages and disadvantages (summarized in Table 3), but ultimately morbidity and mortality are the most important considerations when choosing which procedure to use. Systematic comparisons of the different techniques are needed to which is superior or which is more suitable for certain subpopulations of patients.

The issues of factor replacement and length of hospitalization have yet to be settled. The studies

Table 3. Relative advantages of three approaches to liver biopsy.

Criteria	Percutaneous	Transjugular	Laparoscopic
Cost	X		
Number of passes to obtain adequate tissue	X		X
Measurement of hepatic venous wedge pressure		X	
Haemostasis			X
Direct visualization of liver			X
Widely available	X		

reviewed used a number of different regimens. Continuous infusion seemed to provide higher factor levels compared with intermittent bolus infusions [36,37]. Whether or not this is associated with fewer complications is entirely unknown. Is the use of tranexamic acid beneficial? Some patients were hospitalized for as little as 24 h, but some institutions monitored uncomplicated biopsies in haemophiliac patients for more than 5 days. What criteria should be used to make decisions about discharge? Properly designed studies are required to address these issues. The answers to these questions may ultimately reduce the cost of the procedure in this population without compromising safety.

All the studies which were evaluated, excluded patients with haemophilia that had significant inhibitors, except for the report by DiMichele. DiMichele *et al.* reported that haemostasis was achieved [38] with intravenous desmopressin acetate in one patient with mild haemophilia A who had a high titre inhibitor. This patient was one of three who complained of abdominal pain, but no significant intervention was required. This raises the possibility that patients with inhibitors may undergo liver biopsy. Studies are needed to evaluate the role of liver biopsy in this special population.

Conclusion

Liver biopsy plays a pivotal role in the management of patients with a variety of liver diseases, including chronic HCV. The major risk of the procedure is the potential for significant haemorrhagic complications. Although the data are limited, the procedure does not appear to pose excessive risk to the patient with inherited disorders of coagulation, provided that adequate haemostasis can be achieved prior to the liver biopsy and the procedure is performed by an experienced individual. This requires close coordination of care between the hepatologist and the haematologist. Indications for liver biopsy should be the same in patients with haemophilia as in other populations.

Recommendations

1 Inherited disorders of coagulation are not absolute contraindications to liver biopsy,
2 the value of a liver biopsy in individuals with haemophilia should be weighed against the costs and potential risks,
3 the best factor replacement strategies are not known, but this should encourage close collaboration between the haematologist and hepatologist,
4 More research is required to better define the role of liver biopsy in patients with inherited disorders of coagulation, including those with inhibitors.

Acknowledgements

This study was supported in part by grants from the National Heart Lung and Blood Institute, National Institutes of Health, Minority Investigator Research Supplements, RO1 HL 64817–01 (Michael W. Fried, PI); National Institutes of Health, RO1 AI 49508–01 (Kenneth E. Sherman, PI), National Cancer Institute and RTI International, N01-CP-01004 (James J. Goedert and Barbara L. Kroner, PI); Roche Laboratories; and Hemophilia of Georgia.

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